REMARKS

Favorable reconsideration and allowance are respectfully requested. Claims 123-127, 133-173 and 177-180 have been withdrawn. Claims 1-123 and 128-132 have been cancelled. Claims 174-176 are pending in this application.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 174-175 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claim 174 was rejected as indefinite in the recitation of "a second single chain polypeptide" and claim 175 was rejected as indefinite in the reference to a bispecific antibody because the Examiner contends that it is unclear how the antibody of claim 176, which expresses a single VH and VL region can be bispecific. (Office Action, p. 3).

Applicants have amended claim 176 to refer to a recombinant antibody comprising a first single chain polypeptide. Therefore, the rejection of claim 174 is now moot.

With respect to claim 175, reconsideration of the language used in claims 174-176 is respectfully requested. Applicants respectfully submit that independent claim 176 refers to a recombinant antibody comprising a polypeptide including a VH and VL region. Claim 174, which depends from claim 176, adds to this concept in that it further comprises yet another polypeptide comprising VH and VL regions. Thus, taken together, the antibody of claim 174 includes at least two polypeptides comprising VH and VL regions. As such, it is perfectly reasonable that claim 175 further requires that the antibody of claim 174 is bispecific because contrary to the Examiner's comments in the Office Action, the antibody of claim 174 includes all of the essential elements required of a bispecific antibody.

Rejection Under 35 U.S.C. § 112, First Paragraph: Alleged Lack of Written Description

Claims 174-176 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to

reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner contends that claims 174-176 are directed to an antibody conjugate comprising a VH region of one antibody conjugated to the VL region of another antibody, the regions joined to one another by any method and resulting in an antibody conjugate of any structure. The Examiner alleges that without any structural knowledge, one skilled in the art would be unable to make and use such antibody conjugates. (Office Action, pp. 3-4).

Applicants respectfully traverse and submit that the specification provides ample disclosure to reveal to the skilled artisan that the Applicants were in possession of the claimed invention as of the filing date. The Examiner's attention is directed to pages 15-16 of the specification, which describe various constructs for antibodies of the present invention, including, without limitation, antibodies and methods of making the same comprising the steps of: (i) expressing a gene having the sequence: VL antibody 1-S-VH antibody 2, and (ii) expressing a gene having the sequence: VH antibody 1-S-VL antibody 2, (iii) combining the products of steps (i) and (ii), and (iv) isolating the bispecific antibody, wherein -S- is a linker sequence. That portion of the specification also discloses a method of synthesizing a bispecific antibody comprising the steps of: (i) expressing a gene having the sequence: VL antibody 2-S-VH antibody 1, and (ii) expressing a gene having the sequence: VH antibody 2-S-VL antibody 1, (iii) combining the products of steps (i) and (ii), and (iv) isolating said bispecific antibody, wherein -S- is a linker sequence.

See also page 94 et seq. of the specification, which discloses the use of antibodies to activate prodrugs according to the present invention. In particular, the specification states that the antibodies or active fragments thereof used in the present invention are those of the prior art

(see, inter alia, the Background of the Invention) and those made using the novel haptens described throughout the specification with the techniques known to those skilled in the art of making catalytic antibodies (see e.g., U.S. Patent Nos. 4,963,355, 4,888,281 and 4,792,446). The targeting component of the targeting and activating compounds of the invention includes any agent which selectively binds or concentrates on or in the vicinity of a specific cell population, for example, any antibody or other compound which binds specifically to a tumor-associated antigen (other examples include hormones, growth factors, substrates, or analogs of enzymes, etc.). A non-limiting list of target cell populations is provided on pages 94-95. At page 95 et seq. the specification describes the use of antibodies that bind antigens that are expressed in high density on tumor cells that do not shed from the tumor. Other binding species may also be used in the present invention, e.g., fusions involving growth factors or fragments thereof, e.g., a fusion of a growth factor or a fragment thereof to one end of an antibody single chain gene construct.

At page 98 et seq., the specification provides detailed guidance regarding the production of bispecific proteins. For example, at page 99, the specification describes the production of bispecific proteins by recombinant DNA technology, e.g., the production of fusion protein constructs comprising an antigen binding region of a targeting protein (which is used to target a specific cell population) linked to an enzyme or antibody. Recombinant DNA methods have been used to express antibody genes in mammalian systems. (Oi, V. T., et al., Proc. Natl. Acad. Sci. USA 80 (1983):825-829; Neuberger, M. S., EMBO 2 (1983):1373-1378). Further expression and recovery of biologically active immunoglobulin proteins (human IgE Fc fragment) from *E. coli* has been demonstrated (Kenten, J. H., et al., Proc. Natl. Acad. Sci. USA 81 (1984):2955-2960) and expression and recovery of whole active antibody has been

demonstrated (Boss, M.A., et al., Nucleic Acids Res. 12 (1984):3791-3799). This was followed by other groups demonstrating the generality of the potential to generate both immunoglobulin binding and effector function activities in *E. coli* (Cabilly, S., et al., Proc Natl. Acad Sci USA 81 (1984):3273-3277; Skerra, A., et al., Science 240 (1988):1038-1040; Better, M., et al., Science 240 (1988):1041-1043). These skills and abilities have also been applied to manipulation of many other genes. Methods of antibody engineering are exemplified in EP194276, in which the heavy chain gene is truncated and various genes are added, including the introduction of the desired enzymatic activity following the procedures outlined in the specification and well-known to those skilled in the art.

Moreover, the generation of antibodies which are bispecific is well-known to the art (Shawler, et al., Immunol. 135 (1985):1530-1535; Kurokawa, T., et a1., Bio/Technology 7 (1989):1163-1167). Examples of the functionality of such bispecific antibodies are the tumor specific antibodies which also bind to metal chelates for use in tumor therapy, and also the bispecific antibodies which bind to tumor cells and T cells (Johnson, M. J., et al., Patent Application EP 369566A, 1990; and Gilliland L.K., et al., Patent Application GB 2197323, 1986). Methods for generation of bispecific antibodies consist of chemical methods of separation and recombination of the antibody chains or by the fusion of the two hybridomas to generate so called quadromas. Generation of smaller binding species has been the goal of much research in antibody engineering. This has led to the development of single chain antibodies, in which the variable (V) region of the two antibody chains are combined into a single molecule using a linker sequence (Patent Application WO 88/01649, Ladner and Bird). This combination of V regions results in expression of a protein which has one of the V regions at the amino terminus and the other V region attached at its COOH terminus via the linker to its amino

terminus. This head to tail, head to tail linkage of V regions has been described with both V light chain - V heavy chain and V heavy chain - V light chain orientations. The utility of these systems has been developed with the addition to single chain antibodies of other proteins (Vijay, et al., Nature 339 (1989):394-397). This format, for the addition of other proteins to the end of single chain antibodies, is used for the production of similar molecules making use of desired enzyme genes to affect these constructions. This results in the production of molecules having the desired properties of antibody binding and enzymatic activity in a small molecule ideally suited for therapy.

A detailed description of a method of producing an antibody according to the present invention is provided on page 101 et seq. of the present specification. In addition, methods of producing humanized antibodies, methods of generating antibody expression vectors, and methods of screening for a desired activity are described on page 102 et seq. of the instant specification.

The MPEP clearly states that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). An applicant shows possession of an invention "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was

complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it")." (MPEP 2163(I)).

Applicants submit that the claimed method is described in the specification as outlined above in a sufficient detail to satisfy the requirements of the first paragraph of 35 U.S.C. § 112 (See MPEP 2163.02, "Standard for Determining Compliance with the Written Description Requirement"). When one considers the high degree of skill in the art, one will readily appreciate that Applicants have provided sufficient details regarding the antibody, its components and methods of making such antibodies and that Applicants have provided sufficient detail and defining characteristics for the claimed features to distinguish the invention.

The MPEP clearly states:

> The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. **The examiner has the initial burden of presenting by a preponderance of**

> **evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims.** *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

(MPEP 2163.04, emphasis added.)

Applicants respectfully submit that the Examiner has not met his burden. The Examiner takes issue with the breadth of the instant claims, without reasonably considering whether that breadth is supported by the instant specification in context, i.e., would one skilled in the art recognize in the instant disclosure a description of the invention defined by the claims. Contrary to the Examiner's assertions, the present specification provides extensive disclosure of the various methods used to prepare the claimed antibodies. Still further, the level of skill in the art is high, such that given the extensive disclosure in the specification, the skilled artisan would readily appreciate how to apply the instant invention to other systems.

"In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." *Reagents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); see also, MPEP 2163 (III-3(a)), page 2100-179, left-hand column. Still further, MPEP 2163 (III-3(a)) clearly states that "although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession." As explained by the Federal Circuit, "there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known

structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005) ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.). For example, a disclosure of unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention"). (MPEP 2163 III-3(a)).

Applicants respectfully submit that it is improper to reject claims on the ground that the specification does not support the claims when the terms of the claim are no broader than the broadest description of the invention in the specification and there is no reason to challenge the operativeness of the subject matter embraced by the claims. *Ex parte Altermatt*, 183 U.S.P.Q. 436 (POBA 1974).

In view of the foregoing remarks, Applicants respectfully submit that the written description rejection should be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph: Enablement

Claims 174-176 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. The Examiner alleges that the specification does not enable the production of any antibody conjugate as claimed. (Office Action, p. 5).

Applicants traverse and respectfully submit that the "enablement" prong of the first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement. Whether this is achieved by illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971). An assertion by the Patent Office that the enabling disclosure is not commensurate with the scope of the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. *In re Dinh-Nguyen*, 492 F.2d 856, 181 USPQ 46 (CCPA 1974); *In re Bowen*, 492 F.2d 859, 181 USPQ 48 (CCPA 1974); *In re Armbruster*, 512 F.2d 676, 185 USPQ 152 (CCPA 1975). Moreover, there is no requirement that an applicant provide a working example of his invention. See *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

MPEP 2164.01 (a) enumerates a number of factors for determining whether experimentation is undue. The Applicants assert that considering all of these factors the experimentation inherent in antibody generation and in the generation of antibodies according to the invention is not undue. In the instant specification there is considerable detail, direction and guidance, for generating antibodies as claimed. The extensive disclosure is outlined above in great detail and the skill in the art is high. When the disclosure is given careful consideration by a skilled artisan, it would be apparent that the quantity of experimentation required to reduced the invention to practice is not undue.

Enablement is not precluded by the necessity for some experimentation such as routine screening, However, experimentation needed to practice the invention must not be undue experimentation. The key word is "undue" not "experimentation." *In re Wands,* 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in

question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands,* 858 F.2d 731, 737, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988)." (MPEP 2164.06). "The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ 2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

The generation of antibodies such as those claimed, like the generation of conventional antibodies, requires a certain amount of experimentation to screen for antibodies with the appropriate activity and may not always be successful. In *In re Wands,* 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988), the Federal Circuit held that such experimentation, when carried out for generation of conventional monoclonal antibodies, is reasonable and not undue because of the high level of skill in the pertinent art and, also, because of the considerable direction and guidance provided in the specification on how to practice the invention. Similarly, the skill level in the art of generating antibodies is high and the instant specification presents a detailed description for the generation and screening of antibodies for both *in vitro* and *in vivo* use, including a prescribed algorithm for designing haptens. The detailed screening procedures provided in the specification assure a reasonable expectation of success in obtaining the appropriate antibodies. Such experimentation is reasonable and <u>not</u> undue.

Consequently, Applicants submit that in view of the high state of the relevant art, the disclosure of the instant specification is sufficient to satisfy the enablement requirements of Section 112.

Applicants respectfully submit that the rejection of claims 174-176 under the enablement prong of 35 U.S.C § 112, first paragraph, is improper and should be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 174-176 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Novotny et al., PNAS (1985) 82: 4592-96 ("Novotny"). In addition, claims 174-176 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Scott et al., J. Immun. (1989) 143: 293-98 ("Scott"). The Examiner argues that Novotny and Scott each teach antibodies comprising a VH region of one antibody fragment conjugated to a VL region of another antibody fragment. (Office Action, p. 8). Applicants respectfully traverse.

Novotny studied the conformational features of the VL and VH domains by comparing the crystallographic coordinates of human Fab fragments of NEW, KOL and MCPC 603, as well as VL-VL dimers RHE and REI, and Bence Jones protein MCG. Novotny does not physically construct an antibody comprising the VH domain of one antibody and the VL domain of another antibody. Novotny simply compares the crystallographic coordinates of various antibody fragments. Novotny does not teach or suggest a monoclonal antibody comprised of the VH domain of one antibody and the VL domain of another.

Scott is also distinguishable. Scott purified serum anti-Hib-PS antibodies to monoclonality and identified the VH and VL gene families expressed in this repertoire. Therefore, any one antibody isolated and identified by Scott includes a VH from one antibody and a VL from the same antibody. While a number of anti-Hib-PS antibodies were analyzed by Scott, the VH and VL regions in those antibodies were always from the same antibody. Scott does not engineer antibodies to include a VH region from one antibody and a VL region from another. For at least this reason, Scott does not anticipate the instant claims.

Accordingly, Applicants respectfully request that the anticipation rejections under 35 U.S.C. § 103(b) be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, reconsideration of Claims 174-176 pending in this application and allowance are earnestly solicited.

No additional fees are believed due except for the fee for a three-month extension of time. However, the Director is hereby authorized to charge any required fees and credit any overpayments to Deposit Account No. 50-0540.

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Respectfully submitted,

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